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NEW CRYSTAL FORM

Field of the Invention

This invention relates to a new solid form of a drug and to processes for obtaining the drug.

Background of the invention

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also important to be able to provide the drug in a form, which is as chemically pure as possible.

Amorphous materials may present significant problems in this regard. For example, such materials are typically difficult to handle and to formulate, provide for unreliable solubility, and are often found to be unstable and chemically impure.

The skilled person will appreciate that, if a drug can be readily obtained in a stable crystalline form, the above problems may be solved. The crystalline form of the substance is in most of the cases more stable than the corresponding amorphous material, see for example Oberholtzer, E. R. & Brenner, G. S., *J. Pharm. Sci.*, **68** (1979), 863, Carstensen, J. T. & Morris, T., *J. Pharm. Sci.*, **82** (1993), 657, Kitamura, S., Miyamae, A., Koda, S. & Morimoto, Y, *Int. J. Pharm.*, **56** (1989), 125, and Pfeiffer, R. R., Engel, G. L. & Coleman, D., *Antimicrob. Agents Chemoter*, **9**, (1976), 848.

Thus, in the manufacture of commercially viable, and pharmaceutically acceptable, drug compositions, it is important, wherever possible, to provide a drug in a substantially crystalline, and stable form.

It is to be noted, however, that this goal is not always achievable. Indeed, typically, it is not possible to predict, from molecular structure alone, what the crystallisation behaviour of a compound will be. This can usually only be determined empirically.

Prior Art

International patent application WO 95/30641 discloses 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate and a process for its synthesis.

Whether it is possible to provide 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)-amino]phenyl}acetate in a crystalline form is not disclosed in WO 95/30641. Furthermore, no information is provided in relation to how this compound may be obtained in such a form and, more particularly, how it may be obtained in a chemically, and/or solid, stable form.

Disclosure of the Invention

We have found that 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}-acetate may be readily obtained in a form that is both substantially crystalline and stable.

Thus, according to a first aspect of the invention there is provided 2-[2-(nitrooxy)ethoxy]-ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate in a substantially crystalline form (hereinafter referred to as "the compound of the invention").

Further aspects of the invention there is provided the compound of the invention in the form of an anhydrate. The preparation, and characterisation, of the anhydrate form of the compound of the invention are described hereinafter.

Although we have found that it is possible to produce 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate in a form which is more than 90 % crystalline, by "substantially crystalline" we include greater than 50 %, preferably greater than 60 %, and more preferably greater than 70 % crystalline. The "degree (%) of crystallinity" may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such a solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used as complementary methods.

The compound of the invention may be characterised by its unit cell (see Example 1).

According to a further aspect of the invention, there is provided a stable form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate .

The term "stability" as defined herein includes chemical stability and solid state stability.

By "chemical stability", we include that the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

By "solid state stability", we include that the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, recrystallisation, solid state phase transition, hydration, dehydration, solvatisation or desolvatisation).

Examples of "normal storage conditions" include temperatures of between minus 80 and plus 50°C (preferably between 0 and 40°C and more preferably ambient temperature, such as between 15 and 30°C), and pressures of between 0.1 and 2 bars (preferably atmospheric pressure), for prolonged periods, preferably at least three years. Under such conditions, the compound of the invention may be found to be less than 15 %, more preferably less than 10 %, and especially less than 5 %, chemically degraded/decomposed, or solid-state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature and pressure represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).

The term "normal storage conditions" may also include relative humidities of between 5 and 95 %, preferably 10 to 75 %, measured at a temperature of about 25°C.

The compounds of the invention may be obtained advantageously by crystallising 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate .

According to a further aspect of the invention, there is provided a process for the production of a compound of the invention which comprises crystallising 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate.

Although 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate may be crystallised in the presence or absence of a solvent system. Other examples of crystallisation include crystallisation from a melt, under supercritical conditions, or achieved by sublimation, preferably the crystallisation is from an appropriate solvent system.

We have found that it is possible to obtain crystalline 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate *via* crystallisation, advantageously following dissolution and/or suspension of the compound.

Crystallisation of compounds of the invention from an appropriate solvent system may be achieved by attaining supersaturation in a solvent system which comprises 2-[2-(nitrooxy)-ethoxy]ethyl{2-[(2,6-dichlorophenyl)amino]phenyl}acetate (e.g. by cooling, by solvent evaporation, *via* the addition of a suitable antisolvent, or by a combination of these methods). Crystallisation may also be effected by decreasing the solubility of the substance by the addition of a salt (such as NaCl).

The solvent system may include one or more organic solvents, such as lower alkyl acetates (e.g. linear or branched C_{1-6} alkyl acetates, such as ethyl acetate, *iso*-propyl acetate and butyl acetate), lower (e.g. linear or branched (C_{2-6}, preferably C_{2-4})) alkyl alcohols (e.g. ethanol, *iso*-propanol), aliphatic and aromatic hydrocarbons (e.g. C_{5-12} aliphatic hydrocarbons, C_{6-10} aromatic hydrocarbons (e.g. isooctane, *n*-heptane and toluene)), dialkyl ketones (e.g. di-C_{1-6} alkyl ketones (e.g. methyl ethyl ketone and methyl *iso*-butyl ketone)), dialkyl ethers (e.g. di-C_{1-6} alkyl ethers (e.g. di-*iso*-propyl ether, *tert*-butyl methyleter)), acetonitrile and 1-methyl-2-pyrrolidinone. Mixtures of any of the above-

mentioned solvents may be used. Organic solvents may also be admixed with water or aqueous solutions.

The skilled person will appreciate that the concentration in solution of the compound that is to be crystallised, the solvent system that is used, and the crystallisation temperatures may influence the crystallisation times. The crystallisation time shall be kept shorter than 48 hours, preferably 2 to 24 hours, and most preferably 2 to 15 hours.

Different crystalline forms may have different solubilities in different organic solvents at any given temperature or in this respect, solvents may be employed as "antisolvents" (i.e. a solvent in which compounds of the invention are poorly soluble), and may thus aid the crystallisation process.

Crystallisations may be performed in lower alkyl alcohols and/or *tert*-butyl methyleter. When linear or branched alkyl acetates, such as ethyl acetate, *iso*-propyl acetate and butyl acetate, ketones such as acetone, 4-methyl-2-pentanone, aromatic hydrocarbons such as toluene and 1-methyl-2-pyrrolidinone are used as solvent and an antisolvent is needed; i.e. water, lower alkyl alcohols (ethanol, isopropanol) or aliphatic hydrocarbons (isooctane, *n*-heptane).

Crystallisation may be performed directly after the reaction or after an extraction.

When the crystallisation takes place from a reaction solution in which 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate has been formed, suitable solvents include 1-methyl-2-pyrrolidinone, dimethyl sulphoxide, N, N-dimethylformamide and tetrahydrofuran together with an antisolvent chosen from the group of isooctane, *n*-heptane and water.

The crystallisation may also take place after an extraction of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate from a reaction mixture. Suitable solvents

for the extraction include linear or branched alkyl acetates, 4-methyl-2-pentanone, 2-butanone and toluene. An antisolvent, such as, isooctane, *n*-heptane and water will be needed to generate supersaturation.

Further purification of the compound may be effected by recrystallisation and/or slurrying. The recrystallisation may be from an appropriate solvent system (e.g. linear or branched alkyl acetates, such as ethyl acetate, *iso*-propyl acetate and butyl acetate, ketones such as acetone, 4-methyl-2-pentanone, aromatic hydrocarbons such as toluene and 1-methyl-2-pyrrolidinone), which may include antisolvent (e.g. water, a lower alkyl alcohols (ethanol, *iso*-propanol) or aliphatic hydrocarbons (isooctane, *n*-heptane) or a combination of these solvents).

The compound of the invention may be isolated using techniques, which are well known to those skilled in the art, for example decanting, filtering or centrifuging.

We have found that, by employing the crystallisation process as described herein, it is possible to produce the compound of the invention with a chemical purity which is above that of the 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate which is to be isolated in the first instance.

When the compound of the invention is crystallised, or recrystallised, as described herein, the resultant compound is in a form, which has the improved chemical and solid state stability mentioned herein before.

Pharmaceutical Preparations and Medical Use

In another aspects the present invention provides formulated pharmaceutical formulations comprising, as active ingredient, a therapeutically effective amount of a pharmaceutically acceptable salt of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino] phenyl}-acetate, optionally in association with diluents, excipients or carriers.

According to the present invention the compounds of the invention will normally be administered orally, rectally or parenterally in a pharmaceutically acceptable dosage form. The dosage form may be solid, semisolid or liquid preparation. Usually, the active substance will constitute between 0.1 and 99 % by weight of the preparation, more specifically between 0.5 and 20 % by weight for preparations intended for injection and between 0.2 and 80 % by weight for preparations suitable for oral administration.

The pharmaceutical formulations comprising the crystal form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate are manufactured by pharmaceutical conventional techniques.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.001-100 mg/kg bodyweight for parenteral administrations and about 0.01-100 mg/kg bodyweight for other administration routes.

The crystal form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}-acetate can be used to the treatment of pain and inflammation. The wording "pain" is intended to include, but not limited to, nociceptive and neuropathic pain or combinations thereof; acute, intermittent and chronic pain; cancer pain; migraine and headaches of similar origin. The wording "inflammation" is intended to include, but not limited to, rheumatoid arthritis; osteoarthritis; and juvenile arthritis.

Brief description of the drawing

Figure 1 shows an X-ray powder diffractogram for the crystalline form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate of Example 1.

The examples that follow will further illustrate the preparation of the compound of the invention, according to the different process routes. These examples are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

Examples

General Procedures

X-ray powder diffraction analysis (XRPD) was performed on samples prepared according to standard methods, for example those described in Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R.L. (1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley & Sons, New York; Bunn, C.W.(1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. & Alexander, L.E. (1974), *X-ray Diffraction Procedures,* John Wiley and Sons, New York. X-ray analyses were performed using a Philips X'Pert MPD diffractometer.

Differential scanning calorimetry (DSC) was performed using a Perkin Elmer DSC7 instrument, according to standard methods, for example those described in Höhne, G. W. H. *et al* (1996). *Differential Scanning Calorimetry*, Springer, Berlin.

Thermogravimetric analysis (TGA) was performed using a Perkin Elmer TGA7 instrument.

The form prepared in accordance with Example 1 below showed essentially the same XRPD diffraction pattern and DSC and TGA thermograms as other Examples disclosed below, when it was clear from the relevant patterns/thermograms (allowing for experimental error) that the same crystalline form had been formed. Thus, limits of experimental error for DSC onset temperatures may be in the range ±5°C (e.g. ±2°C), and for XRPD distance values may be in the range ±2 on the last decimal place.

Synthesis of the anhydrate of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate

Example 1

0.3 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 0.9 ml toluene into a 4 ml test tube. The test tube was placed on a magnetic stirrer at ambient temperature. After all substance was dissolved 1.8 ml isooctane was added 0.3 ml-wise. Crystallization started after all isooctane had been added. 4.5 h after crystallization had started the crystals were filtered using vacuum. The tube was rinsed with 0.3 ml isooctane. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 80.6%.

The crystals were analyzed by XRPD, DSC and TGA. The XRPD gave the result tabulated in Table 1 and shown in Figure 1. The DSC thermogram showed a sharp melting point at 72°C and the TGA thermogram showed that the substance did not contain any significant amounts of solvents.

D /Å	Relative Intensity		D/Å	Relative Intensity
12.7	M		3.52	M
8.7	W		3.49	M
8.1	W		3.44	W
6.3	S		3.41	VS
5.94	M		3.31	W
5.91	M		3.28	M
5.58	M		3.17	S
5.34	M		3.15	S
5.05	W		3.13	W
4.50	S		3.06	M
4.48	S		3.04	W

4.38	M		2.97	M
4.35	M		2.96	M
4.28	M		2.81	W
4.23	S		2.70	M
4.08	S		2.68	M
4.06	S		2.64	M
3.96	S		2.60	W
3.78	S		2.54	W
3.76	S		2.43	W
3.55	W			

Table 1: X-ray powder diffraction data for 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate. The main peaks, with positions and relative intensities have been extracted from the diffractogram in Figure 1. The relative intensities are given as VS = Very Strong, S = Strong, M = medium, W = Weak. Only peaks below $2\theta = 40°$ have been included. Some additional very weak peaks found in the diffractogram have been omitted from the table.

All peaks can be indexed with the monoclinic unit cell : a = 13.79 Å, b = 11.90 Å, c = 13.01 Å, $\alpha = 90°$, $\beta = 94.0°$, $\gamma = 90°$.

Example 2

0.3 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 0.9 ml methyl isobutyl ketone into a 4 ml test tube. The test tube was placed on a magnetic stirrer at ambient temperature. Additional 0.3 ml 4-methyl-2-pentanone was necessary to dissolve all substance. Thereafter 1.8 ml isooctane was added 0.3 ml-wise. Crystallization started after all isooctane was added. 4 h after crystallization had started the crystals were filtered using vacuum. The tube was rinsed with 0.3 ml isooctane. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 44.1 %.

The crystals were analyzed by XRPD, DSC and TGA. The results were essentially the same as those exhibited by the form obtained according to Example 1.

Example 3

2.5 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 7.5 ml butyl acetate into a 100 ml jacketed reactor. The reactor was heated to 35°C to dissolve all substance. Thereafter a temperature profile was started: the temperature was lowered to 20°C in 1.5 h and then kept for 0.5 h at 20°C. At 20°C 15 ml isooctane was added dropwise. Crystallization started after 12 ml isooctane was added. The temperature was lowered further to 0°C in 3 h. After 0.5 h at 0°C the crystals were filtered using vacuum. The reactor was rinsed with 7.5 ml cooled isooctane. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 91.6%.

The crystals were analyzed by XRPD, DSC, TGA, LC, and GC. The results from XRPD, DSC and TGA were essentially the same as those exhibited by the form obtained according to Example 1. LC showed a purity of 99.12 area%, GC showed 0.01 w/w% isooctane and 0.10 w/w% butylacetat. The starting material had a purity of 98.42 area% and contained 0.13 w/w% ethyl acetate.

Example 4

0.5 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 1.5 ml tert-butyl methyl ether into a 4 ml test tube. The tube was placed into an oil-bath. Agitation was provided by a magnetic stirrer. The oil bath was heated until a clear solution was obtained in the test tube. This was the case at 40°C. Thereafter the oil bath temperature was again lowered to 20°C. The mixture was held stirred over night and crystals were formed. The crystals were filtered using vacuum. The tube was rinsed with 0.3 ml tert-butyl methyl ether. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 77 %.

The crystals were analyzed by XRPD, DSC and TGA. The results were essentially the same as those exhibited by the form obtained according to Example 1. They showed

essentially the same XRPD pattern as those exhibited by the form obtained according to Example 1.

Example 5

0.5 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 1.5 ml butanol into a 4 ml test tube. The tube was placed in an oil-bath. Agitation was provided by a magnetic stirrer. The oil bath was heated until a clear solution was obtained in the test tube. This was the case at 60°C. Thereafter the test tube was placed on a magnetic stirrer at ambient temperature. Crystallization started immediately. After 2.5 h the crystals were filtered using vacuum. The tube was rinsed with 0.3 ml butanol. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 94 %.

The crystals were analyzed by XRPD, DSC and TGA. The results were essentially the same as those exhibited by the form obtained according to Example 1.

Example 6

0.5 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 1.5 ml isopropanol into a 4 ml test tube. The tube was placed in an oil-bath. Agitation was provided by a magnetic stirrer. The oil bath was heated until a clear solution was obtained in the test tube. This was the case at 60°C. Thereafter the test tube was placed on a magnetic stirrer at ambient temperature. Crystallization started immediately. After 2.5 h the crystals were filtered using vacuum. The tube was rinsed with 0.3 ml isopropanol. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 96 %.

The crystals were analyzed by XRPD, DSC and TGA. The results were essentially the same as those exhibited by the form obtained according to Example 1.

Example 7

0.5 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 2.5 ml ethanol into a 4 ml test tube. The test tube was placed on a magnetic stirrer at ambient temperature. The slurry in the test tube was stirred over night. The crystals were filtered using vacuum. The tube was rinsed with 0.6 ml ethanol. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 93.4 %.

The crystals were analyzed by XRPD, DSC and TGA. The results were essentially the same as those exhibited by the form obtained according to Example 1.

Example 8

0.5 g of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate was charged together with 2.5 ml isooctane into a 4 ml test tube. The test tube was placed on a magnetic stirrer at ambient temperature. The slurry in the test tube was stirred over night. The crystals were filtered using vacuum. The tube was rinsed with 0.3 ml isooctane. The crystals were thereafter dried in a vacuum oven at 35°C. The yield (based on the amount left in the mother liquor) was 99.1 %.

The crystals were analyzed by XRPD, DSC and TGA. The results were essentially the same as those exhibited by the form obtained according to Example 1.

Abbreviations:

D	distance measured in Å [Ångström]
DSC	differential scanning calorimetry
FT-IR	Fourier-transformed infra red spectroscopy
NMR	Nuclear magnetic resonance
TGA	thermogravimetric analysis
XRDP	X-ray powder diffractogram

Claims

1. A substantially crystalline form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)- amino]phenyl}acetate.

2. A stable form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]-phenyl}acetate.

3. A compound as claimed in any one of Claims 1 to 2, which is in the form of an anhydrate.

4. A compound as claimed in Claim 1 characterised by the following major peaks in its X-ray powder diffractogram

D /Å	Relative Intensity		D/Å	Relative Intensity
12.7	M		3.52	M
8.7	W		3.49	M
8.1	W		3.44	W
6.3	S		3.41	VS
5.94	M		3.31	W
5.91	M		3.28	M
5.58	M		3.17	S
5.34	M		3.15	S
5.05	W		3.13	W
4.50	S		3.06	M
4.48	S		3.04	W
4.38	M		2.97	M
4.35	M		2.96	M
4.28	M		2.81	W
4.23	S		2.70	M
4.08	S		2.68	M
4.06	S		2.64	M
3.96	S		2.60	W

3.78	S		2.54	W
3.76	S		2.43	W
3.55	W			

5. A compound as claimed in Claim 1 characterised by having a monoclinic unit cell with parameters

a=13.79 Å, b=11.90 Å, c=13.01 Å, α=90°, β=94.0°, γ=90°.

6. A process for the production of a compound as claimed in any one of Claims 1 to 5, which comprises crystallising 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)-amino]phenyl}acetate.

7. A process according to Claim 6 comprising the following steps:

a) dissolving the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate in a solvent;

b) crystallising the compound by adding an anti-solvent;

c) isolating the crystals formed, and optionally;

d) recrystallising the crystals formed in step b), or isolated in step c).

8. A process according to Claim 6 comprising the following steps:

a) dissolving the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate in a solvent;

b) crystallising the compound by evaporation of the solvent;

c) isolating the crystals formed, and optionally;

d) recrystallising the crystals formed in step b); or isolated in step c).

9. A process according to Claim 6 comprising the following steps:

a) dissolving the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate in a solvent;
b) crystallising the compound by cooling;
c) isolating the crystals formed, and optionally;
d) recrystallising the crystals formed in step b); or isolated in step c).

10. A process according to Claim 6 comprising the following steps:

a) dissolving the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate in a solvent;
b) crystallising the compound by a combination of adding a anti-solvent, cooling and evaporation;
c) isolating the crystals formed, and optionally;
d) recrystallising the crystals formed in step b); or isolated in step c).

11. A process according to Claim 6 comprising the following steps:

a) crystallising the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate directly from the reaction solution by adding an anti-solvent;
b) isolating the crystals formed, and optionally;
c) recrystallising the crystals formed in step a), or isolated in step b).

12. A process according to Claim 6 comprising the following steps:

a) crystallising the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate directly from the reaction solution by cooling;
b) isolating the crystals formed, and optionally;

c) recrystallising the crystals formed in step a); or isolated in step b).

13. A process according to Claim 6 comprising the following steps:

a) crystallising the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate directly from the reaction solution by evaporation;

b) isolating the crystals formed, and optionally;

c) recrystallising the crystals formed in step a); or isolated in step b).

14. A process according to Claim 6 comprising the following steps:

a) crystallising the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate directly from the reaction solution by adding an anti-solvent, cooling or evaporation or a combination of these;

b) isolating the crystals formed, and optionally;

c) recrystallising the crystals formed in step a); or isolated in step b).

15. A process according to claim 6 comprising the following steps;

a) extracting the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate from the reaction solution into a solvent;

b) crystallising the compound by adding an anti-solvent;

c) isolating the crystals formed, and optionally;

d) recrystallising the crystals formed in step b), or isolated in step c).

16. A process according to claim 6 comprising the following steps;

a) extracting the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate from the reaction solution into a solvent;
b) crystallising the compound by cooling;
c) isolating the crystals formed, and optionally;
d) recrystallising the crystals formed in step b), or isolated in step c).

17. A process according to claim 6 comprising the following steps;

a) extracting the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate from the reaction solution into a solvent;
b) crystallising the compound by evaporation of the solvent;
c) isolating the crystals formed, and optionally;
d) recrystallising the crystals formed in step b), or isolated in step c).

18. A process according to claim 6 comprising the following steps;

a) extracting the compound 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate from the reaction solution into a solvent;
b) crystallising the compound by a combination of adding a anti-solvent, cooling and evaporation;
c) isolating the crystals formed, and optionally;
d) recrystallising the crystals formed in step b), or isolated in step c).

19. A process as claimed in any of Claims 6 to 18, wherein the solvent is selected from the group consisting of lower alkyl acetates, lower alkyl alcohols, aliphatic and aromatic hydrocarbons, *tert*-butyl methyleter, dialkyl ketones, acetonitrile, aqueous solutions, and mixtures thereof.

20. A process as claimed in any of Claims 6 to 19, wherein the solvent is selected from the group consisting of C_{1-6} alkyl acetates, C_{2-6} alkyl alcohols, C_{5-12} aliphatic hydrocarbons, C_{6-10} aromatic hydrocarbons, di-C_{1-6} alkyl ethers, di-C_{1-6} alkyl ketones, acetonitrile, water, and mixtures thereof.

21. A process as claimed in any of Claims 6 to 20, wherein the solvent is selected from the group consisting of ethyl acetate, ethanol, *iso*-propanol, isooctane, *n*-heptane, toluene, tertbutylmethyleter, methyl *iso*-butyl ketone, butylacetate, 1-methyl-2-pyrrolidinone, water, and mixtures thereof.

22. A compound obtainable by a process according to any one of Claims 6 to 21.

23. A compound as claimed in any one of Claims 1 to 5 for use as a pharmaceutical.

24. A pharmaceutical formulation including a compound as claimed in any one of Claims 1 to 5 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

25. A formulation as claimed in Claim 24, which comprises an aqueous solution containing the compound.

26. The use of compound as claimed in any one of Claims 1 to 5 in the manufacture of a medicament for the treatment of a condition of pain or inflammation.

27. A method of treatment of a condition of pain or inflammation which method comprises administering a therapeutically effective amount of a compound according to any one of Claims 1 to 5 to a patient in need of such treatment.

Abstract

The present invention relates to a crystal form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate. More specifically, it relates to a crystalline anhydrate of the compound. The present invention also relates to processes for preparing such a form of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate and to pharmaceutical compositions containing it as well as the use of the compound for treatment conditions of pain and inflammation.

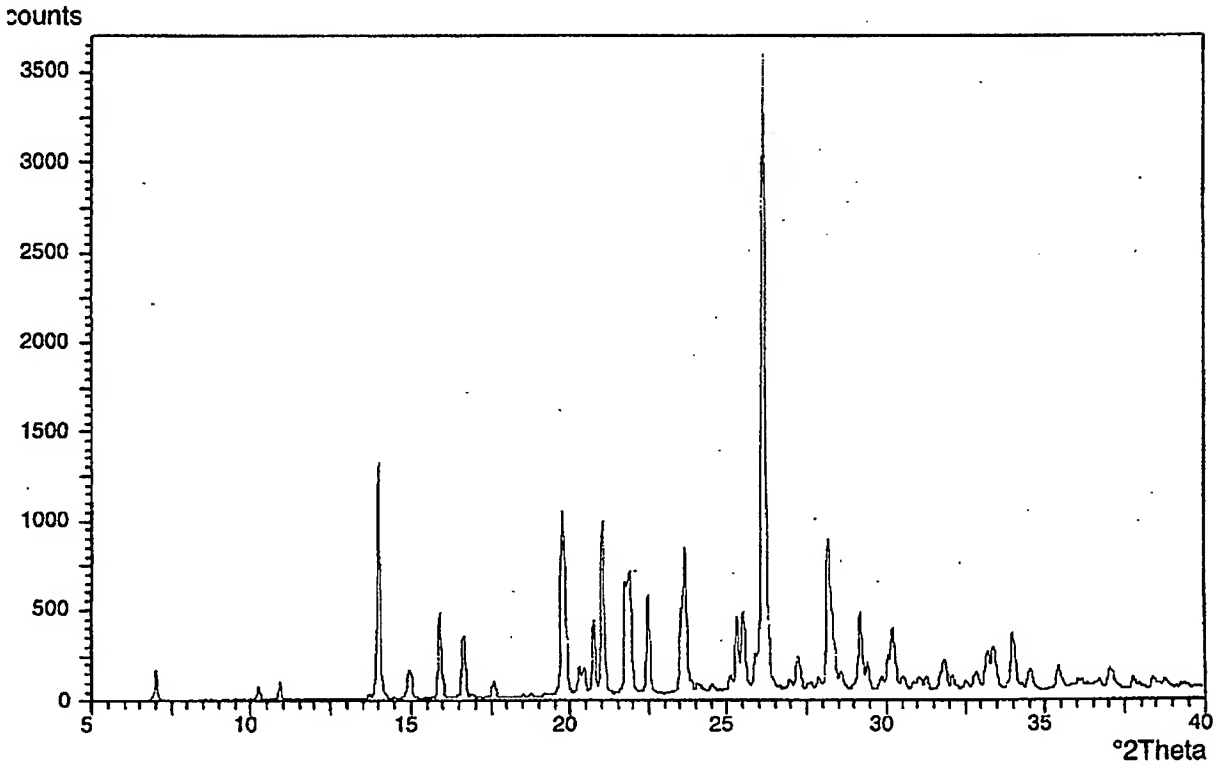

Figure 1 shows a X-ray powder diffractogram for 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate